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EXPLORING THE INFLUENCE OF PARKINSON'S DISEASE ON RELATIONSHIP QUALITY

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EXPLORING THE INFLUENCE OF PARKINSON'S DISEASE ON RELATIONSHIP QUALITY

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my family and friends

&

To all people with Parkinson's disease and their families

ABSTRACT

The aim of this project was to explore how clinical variables affect patients with Parkinson's disease and their partners' relationship quality, health-related quality of life (HRQoL), and caregiver burden.

Fifty-one dyads who had been living together for more than 3 years and aged >55 years were included. Data on motor, non-motor symptom (NMS), relationship quality (mutuality), cognitive decline, activities in daily life (ADL), caregiver burden, and HRQoL were collected.

In study 1, psychometric testing of the translated Swedish version of the mutuality scale (MS) showed that the scale by patients and partners demonstrated high internal consistency ($\alpha \geq 0.93$) and no floor-ceiling effect. Our findings suggest that the Swedish MS is a user-friendly and useful instrument with acceptable psychometric properties. However, more research is warranted regarding the existence of subscales.

Study 2 explores if 1) perceived mutuality by patients and partners differs 2) different factors are associated with patients' and partners' mutuality 3) mutuality is associated with patients' HRQoL and caregiver burden. Our result showed that the dyad rated their own mutuality as high with no differences in total scores. The findings suggest that NMS and high perceived mutuality by the patients are associated with their own HRQoL. High perceived mutuality by partners is associated with caregiver burden. Partners' mutuality was a dominant contributor to patients' mutuality and vice versa. In general, it seems like NMS and mutuality contribute to a larger extent to the deterioration of HRQoL and caregiver burden than motor disabilities.

Study 3 explores if mutuality acts as mediator between clinical variables and patients' HRQoL. Our main findings suggest that when motor disability and NMS are present in everyday/care situations, patients' HRQoL deteriorates because patients' mutuality suffers.

Study 4 explores if mutuality acts as mediator between clinical variables and caregiver burden. The main findings suggest, that when dependency in ADL or decline in cognitive function is present in everyday/care situations, caregiver burden increases because partners' mutuality suffers.

SAMMANFATTNING

Det övergripande syftet med denna avhandling vara undersöka hur Parkinsons sjukdom (PS) påverkar parrelationens kvalitet när en i paret har PS. Femtioen par som levtt ihop i mer än 3 år och var >55 år inkluderades i projektet. Data samlades in avseende motoriska och icke-motoriska symptom, parrelationens kvalitet, kognitiv förmåga, aktiviteter i dagliga livet (ADL), hälso-relaterad livskvalitet (HRQoL) samt anhörig belastning.

I studie 1, översattes och psykometriskt testades skalan "Mutuality" som mäter parrelationens kvalitet. Den svenska versionen visade sig ha hög intern konsistens ($\alpha \geq 0.93$). Ingen golv-tak effekt kunde påvisas. Vår resultat indikerar att den svenska versionen är ett användarvänligt instrument med acceptabel psykometri även om mer forskning behövs avseende subskalor.

I studie 2 undersöktes om 1) patienter och partners upplevelse av parrelationens kvalitet skiljer sig åt 2) det är skillnad på vilka faktorer som är associerade med patienters och partners upplevelse av parrelationen 3) parrelationens kvalitet är associerad med patienters HRQoL och partners upplevelse av belastning. Våra resultat visar att patienter och partnerna upplevde sig ha en stark parrelation och det var ingen skillnad mellan grupperna avseende skalans totala poäng. Icke-motoriska symptom och patienternas egen upplevelse av parrelation hade störst inflytande på HRQoL. Partnernas skattning av parrelationen hade störst inflytande på upplevelse av belastning. Vidare, patienters upplevelse av parrelationen påverkar partners uppevelse av parrelation och vice versa. Överlag indikerade våra resultat att icke-motoriska symptom och parrelationens kvalitet är av större betydelse för HRQoL och upplevd belastning jämfört med motoriska symptom.

I studie 3 undersökte vi om parrelationens kvalitet agerar som en mediator avseende kliniska variabelers effekt på HRQoL. Våra resultat indikerade att motor- och icke-motoriska symptoms negativa effekt på patienternas HRQoL sker pga att relationens kvalitet sjunker hos patienterna.

I studie 4 undersökte vi om parrelationens kvalitet agerar som en mediator avseende kliniska variabelers effekt på partner belastning. Våra resultat indikerar att patienters beroende i ADL och nedsatt kognitiv förmåga har en negativ påverkan på partner belastning pga att relationens kvalitet sjunker hos partnerna.

LIST OF SCIENTIFIC PAPERS

- I. Karlstedt M, Fereshtehnejad SM, Winnberg E, Aarsland D, Lökk J. Psychometric properties of the mutuality scale in Swedish dyads with Parkinson's disease. *Acta neurologica Scandinavica*. 2017;136(2):122-8.
- II. Karlstedt M, Fereshtehnejad SM, Aarsland D, Lökk J. Determinants of Dyadic Relationship and Its Psychosocial Impact in Patients with Parkinson's Disease and Their Spouses. *Parkinsons Disease*. 2017;2017:9.
- III. Michaela Karlstedt, Seyed-Mohammad Fereshtehnejad, Dag Aarsland, and Johan Lökk, Mediating Effect of Mutuality on Health-Related Quality of Life in Patients with Parkinson's Disease," *Parkinson's Disease*, vol. 2018, Article ID 9548681, 8 pages, 2018. <https://doi.org/10.1155/2018/9548681>.
- IV. Michaela Karlstedt, Seyed-Mohammad Fereshtehnejad, Dag Aarsland, and Johan Lökk, Mediating Effect of Mutuality on Caregiver burden in Parkinson's disease partners. Submitted

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LIST OF ABBREVIATIONS

AD	Alzheimer disease
ADL	Activities of daily living (svenska=aktiviteter i dagliga livet)
Beta	Standardized beta coefficients or path coefficients in SEM
CBS	Caregiver burden scale
CFI	Comparative fit index
CI	Confidence interval
GFI	Goodness-of-fit statistics
HRQoL	Health-related Quality of Life
H/Y	Hoehn and Yahr scale
IADL	Instrumental ADL
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQR	Interquartile range
MS	Mutuality scale
MoCA	Montreal Cognitive Assessment
NFI	Normed fit index
NMS	Non-motor symptoms
NMSQuest	Non-motor-symptoms Questionnaire
Pat.MS	Patients' mutuality scale scores
Part.MS	Partners' mutuality scale scores
PCA	Principal component analysis
PD	Parkinson's disease
PDQ8	Parkinson's disease Questionnaire
PDQ8SI	Parkinson's disease Questionnaire Summary Index
PS	Parkinsons sjukdom
RMSEA	Root Mean Square Error of Approximation
TLI	Tucker Lewis index
UPDRS III	Unified Parkinson's motor Disease Rating scale III
QoL	Quality of life
Rho	Spearman correlation coefficient
SD	Standard deviation

SEM	Structural Equation Modeling
VIF	Variance inflation factor

1 INTRODUCTION

Caroline stated: "...we went to the party, but when we had finished dinner, he got cramps in his legs and went out and sat in the car. Nothing worked and we went home. It is frustrating. You miss the rest of the party....dancing and such..... I wouldn't dream of sending him home in a cab and stay at the party" (1)

And

Mary reflected: '...there are so many things he would like to do and knowing he wants to so much, I can't bring myself to go, I cannot do that" (1)

My work as a nurse repeatedly brought me face-to-face with couples living in the shadow of a progressive disease like Parkinson's disease (PD) struggling with their everyday life. On one hand, frustration and hostility were sometimes present in the tone of their voices and in the way they communicate with each other when we were talking about the care situation. On the other hand, I have also met couples dealing with severe disability who seem to maintain some kind of inner strength and love for each other no problem encountered seemed too hard to concur.

This made me curious about the significance of relationship quality especially since dealing with PD symptoms and medication are a huge part of PD families' everyday life and it is well known that PD may negatively influence wellbeing. I also found out by searching the literature that research regarding PD and relationship quality is scarce. There are lessons to be learned and knowledge to be gained with hope to shed a light on the significance of relationship quality in PD care.

2 BACKGROUND

PD is the second most common neurodegenerative disorder after Alzheimer's disease (AD). PD is a complex disorder characterized by motor symptoms such as tremor, rigidity, bradykinesia and postural instability. In addition to motor signs, a wide variety of non-motor symptoms (NMS) are presented and some of them may precede motor signs (2-4). The majority of patients' symptoms start to appear somewhere between the age of 60-70 years and less than 4% is younger than 40 (5). Furthermore, PD is slightly more frequent in men (5). In Sweden the prevalence is estimated to approximately 22 000 and in Stockholm to 196 per 100 000 people (6). Worldwide estimated prevalence of PD is calculated to range between 100-200 per 100 000 people (5). Since an ageing population and an on-going progress of medical treatments are expected, the cost for society will most probably increase (6). Even if advanced medical treatments most likely will improve PD patients' wellbeing, living and coping with advanced treatments are not always without challenges and constraints, neither for patients nor their partners (1).

The exact cause of PD is still unknown. Research so far points to a combination of genetic and environmental factors as the cause of PD. In the central nervous system, dopamine function as a transmitter substance sending signals from one neuron to another. It has been found that PD patients have a substantial loss of dopaminergic neurons in the midbrain, especially within the area of substantia nigra pars compacta(7). The loss of neurons is believed to be caused by accumulation of misfolded α -synuclein protein constituting Lewy bodies in the cytoplasm, leading to a depletion of dopamine. Even if there are discussions where this Lewy pathology starts, the disease is spreading and one hypothesis is that it starts in the gut and over time spreads to higher cortical areas (7-9).

The onset of PD is always insidious with slow development of motor symptoms in no particular order. However, motor symptoms often start in one hand and spread to the limb on the same side and over time also spread to the other side of the body. A typical PD onset is in person who seeks care because of tremor in one hand or because a relative has noticed that the person has reduced arm swing on one side during walks.

Even if NMS such as constipation, sleep behaviour disorder, olfactory deficit, and depression are associated with advanced PD, these symptoms can antecedent the first presentation of motor symptom (8). An extensive review by Chadhuri et al. showed that NMS can emerge from nearly all organ systems ranging from neuropsychiatric, autonomic, urogenital dysfunctions to sleep disturbance as well as other symptoms, sometime categorized as miscellaneous in the literature (table 1) (10).

Table 1. Example of common non-motor symptoms

Neuropsychiatric symptoms	Depression, anxiety, compulsive behaviour, hallucination and cognitive impairment
Autonomic disorders	Urine urgency, nocturia, sweating and orthostatic hypotension, sexual dysfunction
Gastrointestinal symptoms	Dribbling, dysphagia, reflux, vomiting, nausea/gastropares, constipation
Sleep-related symptoms	Difficulties to fall asleep, maintain sleeping during night, vivid dreams, nightmares, restless legs, excessive day time sleepiness
Sensory symptoms	Loss of smell, blurred vision, dry eyes, diplopia, fatigue of eye movements, altered colour vision, decrease sensitivity to contrast vision, feeling of numbness, weakness or spasm and muscle cramps typically in the neck or calf muscle
Other symptoms	Fatigue, weight loss

Consequences of PD are clearly areas deserving further investigation, not only because of increasing societal costs, but also the detrimental effects they have on patients and their partners. The complexity of symptoms and their unpredictability, especially in later stages of the disease, will undoubtedly influence almost all everyday activities performed by the patient. Partners, also suffer from the disease as a result of patients' increasing need of help as well as the pain of seeing a loved one struggling with daily activities (11-13).

2.1 HEALTH-RELATED QUALITY OF LIFE

It is likely that the patients' experience of bradykinesia, rigidity or postural instability makes activities of daily living (ADL) such as getting dressed and walking be perceived as difficult. Likewise, other common instrumental activities of daily living (IADL) such as transportation or managing household chores are often early affected by motor and NMS. Even if there are no universal agreement in how to define HRQoL, it refers to "patient experiences related to health status, including physical, mental, and social aspects as well as judgments, feelings, and reactions associated with them" and is often used for the assessment of health outcome in PD (14, 15). PD symptoms such as gait problem, postural instability, and freezing of gait have been reported to negatively influence patients' HRQoL, also reflecting fear of falling (16, 17).

In addition to motor symptom, NMS are well known to have a negative effect on HRQoL (18-22). It has been suggested that NMS contribute to a larger extent than motor symptoms to

the deterioration of HRQoL (18, 20). Studies have reported that PD patients have between 8-13 NMS and very few patients are completely free of NMS (23-26). A review found that specific NMS showing strong association with HRQoL are depression, anxiety, and cognitive decline. Other symptoms of autonomic dysregulation associated with worse HRQoL are depression, anxiety, and cognitive decline. Other symptoms of autonomic dysregulation associated with worse HRQoL are: orthostatic hypotension, urinary incontinence, insomnia, constipation, dribbling, fatigue, and pain (18). Furthermore, both motor and NMS complications such as wearing-off are negatively associated with perceived HRQoL(27). Thus, using HRQoL as an outcome variable investigating PD patients' relationship quality association with PD symptom and HRQoL, seemed relevant.

2.2 CAREGIVER BURDEN

Not all family members may regard themselves as caregivers especially when PD symptoms are less severe. In this project, some of the partners did not define themselves as caregivers, instead they described themselves as partners in care or care partners.

Nonetheless, the inevitable progression of PD symptoms often results in increased functional dependency and increase need of help in both ADL and IADL. Spouses are often the persons who gradually take over tasks and responsibilities without any training, remuneration or increased support. This can transform the quotidian caregiving in turn leading to caregiver burden (28). Similar to the concept of HRQoL, there is no universal definition of caregiver burden but it refers to the physical, emotional, social, and financial strain that individuals who perform caregiving tasks may experience (15, 28-30). A review reported that caregivers' and patients' own depression may negatively affect caregivers' perceived burden (31). Furthermore, a large amount of studies has reported that the overall experience of NMS and specific NMS such as autonomic dysfunction, fatigue, impaired cognition, hallucinations, pain, and sleep disorders are associated with caregiver burden. Also, motor impairments, complications, falls, severity and disability of PD are associated with elevated caregiver burden (12, 32-38). Overall, caregiver burden seems to be an important and relevant outcome to assess, when exploring the association between relationship quality and PD symptoms.

2.3 MUTUALITY

In most relationships with established roles, caring for each other is an integral part of the relationship. Thus, caregiving can be seen as an extension of caring of each other, including to protect each other's wellbeing (28). Even if close affective relationships could be considered as the norm in caregiving situations, caregiving can take place without this kind of close relationship (39). Mutuality as a concept was introduced and defined by Hirschfeld (40). These results indicated that it is more likely to consider institutionalization of a person with dementia if the caregiver has low perceived mutuality. In contrast, caregivers with high

mutuality are more likely continuing the care for a person with dementia at home. Mutuality defined by Hirschfeld included two components: 1) the ability to find gratification and meaning in the relationship with the person with dementia and from the caregiving situation 2) finding a mutual exchange with the impaired person regardless of what influence the disease has on the care situation (40).

Influenced by Hirschfeld and based on qualitative studies, Archbold et al. defined mutuality as the “positive quality of the relationship between a family caregiver and a care receiver” (41, 42). Mutuality is conceptualized as having four dimensions: love and affection, shared pleasurable activities, shared values, and reciprocity. High scores on the developed instrument, which is intended to measure mutuality, indicate that the relationship between the caregiver and care receiver is characterized by a great deal of love and affection, agreement and shared values, sharing pleasurable activities, and experiences of reciprocal support (41, 42). Even if the definition of mutuality by Archbold et al. has been used in a wide variety of research, few studies have explored mutuality in PD dyads (41, 43).

A review of the literature regarding mutuality and associated factors suggests that mutuality is a protective factor against negative caregiving outcomes shown by the association between higher level of caregivers’ mutuality and lower caregiver burden/strain (42, 44-46). Also, PD caregivers with high perceived mutuality at baseline experienced less strain 10 years later (45). Studies on cancer patients and their caregivers suggest that mutuality may act as a moderator as the presence of both high mutuality and being prepared for increased caregiving demand mitigated perceived caregiving difficulties and mod disturbances (47). Relationship quality has also been proposed, in a sample with PD caregivers (22.1% were paid caregivers), to act as a mediator between behavioural problems and caregiver burden (48).

Caregivers of persons with AD and persons with PD who had provided care for a longer period of time had higher perceived mutuality compared to those with shorter caregiving time (49). The result is in line with other studies and implies that caregivers with high mutuality are more motivated to continue the care of the disabled person (42, 46, 50).

Even if mutuality seems to protect caregivers, mutuality has also been reported to decrease across the stages of PD indicating that PD severity has a negative influence on mutuality (51). The results of prior studies are inconsistent if mutuality changes over time. One study included a mixed sample of patients with AD and PD showed that caregivers’ mutuality did not decrease over a time period of 12 months (49). In contrast, in a sample including older dyads the authors reported that care receivers had higher level of mutuality at baseline compared to their caregivers, but over time care receivers’ mutuality decreased faster. One explanation was that care receivers’ physical ability to engage in joint leisure activities decreased in turn leading to lower perceived mutuality (52).

Previous research also indicates that mutuality and associated factors may differ between patients and partners. For instance, mutuality was reported as a significant predictor of life satisfaction (measurement of HRQoL) of both patients and their caregivers even if caregivers' life satisfaction decreased and stroke patients' life satisfaction increased (53).

Another dyadic study on patients' suffering from heart failure and their caregivers showed that if both the patients and their caregivers had high level of mutuality, they were also more confident regarding patients' self-care. However, there was no partner effect meaning that one member of the dyad did not influence the other member of the dyad (54).

To our knowledge very few quantitative studies have investigated PD patients' experience of relationship quality and associated factors. Nonetheless, a small study including both PD patients and caregivers reported that the experience of personal growth of living with PD was related to better marital quality (55). Another, small study reported that PD patients are more depressed and less satisfied with their marriage (56). Neither motor signs, PD duration, mood symptoms nor HRQoL were associated with patients' and caregivers' relationship quality (56). In contrast, Lyon et al. found significant correlations between caregivers' mutuality and caregiver burden, gait impairment, impaired cognition and PD duration. However, in the subsequent regression analyses including both caregiver variables and patient variables, caregiver burden was the only significant predictor of mutuality (44).

Dyadic qualitative interview studies have described both positive and negative changes of the relationship quality. In general, it seems like PD either brings the couples together or creates a distance between the members of the dyads. This transition towards better or worse relationship had different causes and was handled in different ways (1, 57-59).

Unpredictability of PD symptoms, speech difficulties, less joint social activities, and the way the dyad spent time together were common causes afflicting the relationship (13, 57, 59).

Furthermore, some patients expressed uncertainty and worries about whether the relationship will last or if the partner will start to resent them and leave them when the disease advances and becomes more challenging (59). Altogether, mutuality seems to be an important factor to consider when caring for PD dyads even if more research is warranted especially on how PD symptom influence mutuality.

2.4 STRESS PROCESS MODELS

Since the overarching aim of this project was to gain insight how PD symptoms influence PD patients' and partners' mutuality and the association with psychosocial outcomes. It was necessary to understand the relationship between factors that determine levels of health related outcomes. Without some kind of theoretical framework, we are left with limited

understanding of the association among stressors that accompany disease-related changes. A more thorough understanding of stressors' effect and consequences may yield valuable information and knowledge which can personalize interventions and approaches in the care of PD dyads. Most of caregiving research is based on different stress process models (28, 31, 48, 60). The models often describe complex interactions between patient and caregiver characteristics, features and appraisal of the caregiving situation, intra- and interpersonal resources and all can have direct or indirect effects and determine caregiving outcomes (61). The analyses in this project are mainly guided by a modified stress process model by Judge et al. developed for persons with dementia in combination with the model proposed by Grenwell et al. developed for caregivers (31, 60). Since the overarching aim was to explore the association between PD symptoms, mutuality, HRQoL and caregiver burden the stress process models were used as a guide in our analytic plan regarding the relationship between the included variables. Disease related factors such as motor, NMS, decline in cognitive function and dependency in ADL were chosen as primary stressors which has direct or indirect effects through mutuality on patients' HRQoL and caregiver burden (31, 60).

2.5 RATIONALE

Living with PD can be challenging and a huge part of everyday living concerns assessment of PD symptoms and using different strategies to adjust and avoid wearing off symptoms. Still, the inevitable progressive nature of PD will lead to increasing need of help from other family members which often is the partner. It is reasonable to believe that motor and NMS will influence both patients' and partners' mutuality and be associated with HRQoL and caregiver burden. The review of the literature revealed several knowledge gaps. First, very few studies have explored PD symptoms association with mutuality. Especially patients' perceived mutuality associated with PD symptoms and HRQoL is not fully investigated. Secondly, there is a lack of knowledge about differences between patients' and partners' mutuality and associated PD symptoms. Thirdly, even if there are some studies indicating that mutuality acts as mediator, more research is needed.

3 AIMS

The overall aim of this thesis was to improve knowledge how PD symptoms influence the dyads' mutuality and their association with psychosocial consequences that may appear when one is having PD. For this purpose, we also needed to translate and evaluate psychometric properties of the mutuality scale (MS), which measures the quality of relationship between patients and partners.

Specific aims and hypotheses

Study 1

The aim of this study was to validate and assess psychometric properties of the Swedish version of the MS to evaluate the quality of the relationship between PD patients and their partners

Study 2

The aim of the study was to identify factors associated with patients' and partners' mutuality, patients' HRQoL, and caregiver burden.

We hypothesized that there are

- 1) differences of perceived level of mutuality of patients and partners
- 2) differences in factors associated with the mutuality of patients and partners
- 3) a relationship between patients' and partners' mutuality as well as patients' HRQoL and caregiver burden.

Study 3

Since the relationship between mutuality and patients' HRQoL was not fully explained in study 2, new research questions arose that are addressed in this study. Therefore, the aim of the study was to explore if patients' or partners' mutuality mediated the effect that some clinical variables had on patients' HRQoL.

We hypothesized that motor symptoms, NMS, impaired cognition and dependency in ADL act as primary stressors with direct or indirect effects (mediated) through patients' mutuality and partners' mutuality on patients' HRQoL

Study 4

Since the result of study 2 did not fully explained the relationship between mutuality and caregiver burden, new research questions arose that were addressed in this study. Therefore,

the aim of the study 4 was to explore if patients' or partners' mutuality mediated the effect that some clinical variables had on caregiver burden.

We hypothesized that motor symptoms, NMS, impaired cognition and dependency in ADL act as primary stressors with direct or indirect effects (mediated) through partners' mutuality and patients' mutuality on caregiver burden.

4 MATERIAL AND METHOD

The dyads were recruited during 2014-2015 from movements disorder clinics at Karolinska University Hospital and through advertisement in the journal of the Swedish Parkinson's disease Association.

4.1 ELIGIBILITY

To be included in the project, a specialist in movement disorder should have diagnosed the person with PD. The patient and their partner should be living together as partners for 3 years or more and be aged ≥ 55 . Furthermore, they should not be in the phase of rearing small children or having a partner employed as a caregiver. Other eligibility criteria consisted of no severe medical condition other than PD, which could influence daily life. This was judged by the authors. None of the participants should have major speech difficulties or being a non-native Swedish speaker since this might interfere with the ability to respond to questionnaires. Acceptable cognition based on Montreal Cognitive Assessment scores (≥ 23) was also required.

4.2 PROCEDURE

All self-rated questionnaires were filled out separately and individually at the out clinic or during a home visit, whichever was preferred by the dyads. Time for these meetings was determined by the participants themselves, based on what day and time of and the day best suited them implying that most of the patients were in the "on" status. The dyads filled out the questionnaires in the presence of the author of this thesis, in case of any questions arose. Also, the clinical examinations were performed by the author of this thesis.

We used several standardized questionnaires which are widely used and well validated for research in PD. Sociodemographic data regarding, age, gender, education, income, work status, years of cohabitation, and PD duration were also collected.

4.3 MEASUREMENTS

The mutuality scale (MS) was used to measure the positive quality of the relationship between patients and partners. The scale contains 15 items and is answered using a 5 point Likert scale (0= not all, 4= great deal). Higher scores indicate a relationship characterized by a great deal of love, shared pleasurable activities, shared values and reciprocity (41, 42).

The caregiver's burden scale (CBS) measures the PD partners' reaction to caregiving. The CBS is a 22 items scale and is answered using a 4-point Likert scale. The scale covers domains such as general strain, isolation, disappointment and emotional involvement. Higher scores indicate more feelings of stress in caregiving (62).

Parkinson's disease Questionnaire (PDQ8) measures PD specific health related quality of life. It is comprising of 8 items, using 5-point Likert scale and covers domains as; mobility, activities of daily life, emotional well-being, stigma, social support, cognitions, communication and bodily discomfort. Higher scores indicate high level of problems

Hoehn and Yahr scale (H/Y) was used for staging of PD from 0 = no visible symptoms to 5= bedridden unless assisted of someone (63).

The Unified Parkinson's Disease Rating scale III (UPDRS III), measuring PD specific motor symptoms. The scale covers domains as; facial expressions, speech, sleep positional and intention tremor, rapid alternating movements, rigidity, balance, posture, bradykinesia, as well as gait and ability to move from sitting to standing. The scale contains 14 items and is answered using a 4 point Likert scale. Higher scores indicate more severe motor signs (64).

Non-Motor Symptoms Questionnaire (NMSQuest) it detects PD specific non-motor manifestations in domains such as attention/memory, gastrointestinal, urinary, sexual function and miscellaneous. The scale contains 30 items scored "yes" or "no" (23, 26).

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). It uses information from the partners to assess functional changes associated with cognitive functioning. The scale contains 26 items and is answered using a 5 point Likert scale. Higher scores indicate decline in cognitive functioning (65).

A modified form of Katz index was used to assess the level of dependency in ADL. The scale contains items assessing grooming/dressing, bathing, food intake, toileting, walking/transferring, housekeeping and shopping. The scale is answered using a 4-point Likert scale (0=no help to 3=need all help) and was filled out by the partner. A dichotomous variable (0=independent 1=dependent) was created aiming to assess dependency (66).

Montreal Cognitive Assessment (MOCA). This is a cognitive screening instrument well suited for PD. It covers domains as; immediate and delayed recall, executive function, visospatial processing, language and naming, abstraction and orientation. Scores range from 0-30 points and scores above 26 are considered normal.

4.4 TRANSLATION AND ADAPTATION OF THE MUTUALITY SCALE

In study 1, the MS was translated using forward and backward method. One independent bilingual person whose mother tongue was Swedish translated the English MS into Swedish. Another independent bilingual person whose mother tongue was English translated the Swedish MS back to English. The translation was done with permission of the developer.

The translated versions were then critically reviewed to maintain content validity and ensure linguistic correctness of the scale at a conceptual level. This was done by an expert panel including one professor in medical science, one senior lecturer and one lecturer in nursing science. Two lay persons (one musician and one preschool teacher) evaluated the scale regarding clarity of the items and response format.

4.5 STATISTICAL METHODS

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) and AMOS graphic module version 24 (IBM INC). The level of statistical significance was set to $p < 0.05$ in all analyses.

Several statistical methods have been used and in this chapter the statistical methods that have been used throughout the included studies will be summarized.

For description of continuous variables mean and standard deviation (SD) were used. For categorical variable frequency and percentage were used. Stages of PD assessed by H/Y and dimensions of the MS are presented as medians and interquartile ranges (IQR).

Study 1

To explore the underlying structure of the Swedish MS, separate principal component analyses (PCA) were performed in each group. That is, one PCA was performed on the scale answered by patients and one PCA on the scale answered by partners. To assess the appropriate number of components, eigenvalues, scree plots and number of high loading variables on emerged components were used (67). To assess reliability and internal consistency Cronbach's coefficient, mean inter-item correlation and additional 95 % CI were calculated for the entire scale and the emerged components. Mean inter-item correlation was used together with Cronbach's alpha to assess if mutuality is a broad or a narrow concept (68). A Cronbach's alpha value of > 0.7 was considered as an acceptable value (68). Floor ceiling effects were also calculated for both scales and considered acceptable if less than 15% (69). An independent sample t-test was used to compare the mean MS scores between patients and partners. Validity was tested by assessing if MS scores declined across H/Y stages since this has been demonstrated in prior research (51).

Study 2, 3 and 4

Prior to the main analyses in study 2, 3 and 4. Spearman correlation coefficients (Rho) were used to assess direction and strengths of the correlation between independent variables and outcome variables. Correlation coefficients calculated as 0.1-0.29 were considered as weak, 0.3-0.49 were considered as medium and > 0.5 as strong (70). Furthermore, assumptions of linearity, normality and homoscedasticity were examined through histograms and scatterplots of residuals. Multivariate influential outliers were assessed by using Mahalanobis and Cook's distance (67). To detect suspect multicollinearity, tolerance or variance inflation (VIF) was assessed and tolerance > 0.4 or VIF < 2.5 was considered acceptable.

Study 2

To explore the association between disease related factors, mutuality, and the outcome variables, four regression models were constructed with partners' mutuality, patients' mutuality, patients' HRQoL and caregiver burden as dependent variables (31, 48). Disease related factors and mutuality which had correlations coefficients >0.1 were entered into the constructed regression models. The results of the regression analyses are presented as standardized regression coefficients (beta). Age, gender and education were used for statistical adjustment. If multicollinearity was detected, the independent variables with tolerance <0.5 or rho <0.5 were removed one by one. The independent variable with the highest tolerance, highest adjusted R² and best fit regarding the assumptions of regression analysis remained. We used the Mann-Whitney U test to explore dyadic differences between MS total scores and the original MS dimensions.

Study 3 and 4

Based on the result of study 2 and guided by the proposed stress-process theories our aim was to explore if patients' or partners' mutuality act as a mediator (31, 48, 60).

In study 3 the aim was to explore if the effect of motor, NMS, impaired cognition, dependency in ADL on patients' HRQoL are mediated by patients' or partners' mutuality.

In study 4, the aim was to explore if the effect of motor, NMS, impaired cognition and dependency in ADL on caregiver burden are mediated by patients' or partners' mutuality.

To test our mediation hypotheses structural equational modeling (SEM) with manifest variables was performed. Total, direct and indirect effects were calculated using maximum likelihood estimation and are presented as standardized path coefficients (beta) in the studies. One advantage of using SEM is that direct and indirect effects are simultaneously calculated within the model instead of calculating several regression analyses and stepwise test direct and indirect effects.

The fit of the models was tested using the chi-square test, comparative fit index (CFI), normed fit index (NFI), Tucker-Lewis index (TLI), goodness-of-fit statistics (GFI) and the root-mean-square error of approximation (RMSEA)(71). A model was considered having an acceptable fit when the chi-square value was non-significant and CFI, NFI, TLI, GFI >0.95 and RMSEA <0.05 (71).

To test the indirect effects, the Bias-corrected bootstrap procedure was used. Bootstrapping is a non-parametric resampling procedure which uses a 95% CI to construct confidence intervals for the indirect effects (72). In our studies the 95% CI was determined following 2000 iterations from the sample of 51 participants. When the upper and lower 95% CI are above or below zero, a mediation effect is demonstrated. In contrast, when the upper and lower 95% CI includes zero no mediation effect is demonstrated (72)

We used typology and interpretation proposed by Zhao et al. to classify and understand different types of mediation (73).

4.6 ETHICAL CONSIDERATIONS

Ethical approval was granted before start of this project (registrations number: 2013/1812-31/3) and was done in line with the Helsinki Declaration. Written and oral information about the aim of the study was provided to all participants before the meeting at the out clinic or at the dyads' homes. Questions about the study were followed up before the informed consent was signed and the questionnaire was filled out. This was done to assure that the aim and procedure of the study were understood by the participants. Travel expenses were reimbursed for those participants who lived outside of Stockholm. All questionnaires were coded and the results were only presented at group level to avoid identification.

There are some possible risk of discomforts filling out the questionnaires which could disturb the integrity or the participants or bring up negative feelings about the life situation.

However, all questionnaires have been used in previous research. Furthermore, the participants were informed how to contact the author for questions and concerns. They were also informed that the participation in the study and they could withdraw their consent any time point. The completion of the questionnaires was also voluntary. Each study participant received a study identification and all questionnaires were anonymized, stored and kept in a locked area.

5 RESULTS

5.1 STUDY SUMMARY AND MAIN FINDINGS

When PD occurs in the context of a marriage or other romantic relationship both members of the dyad are affected and the disease may threaten the stability of close relationship (57, 59, 74). Knowledge how PD symptoms affect both members' mutuality may help clinicians to support dyads and pave way for future interventions. Therefore, the overarching aim of this thesis was to improve knowledge how PD symptoms influence the dyads' mutuality and their associations with patients' HRQoL and caregiver burden. This chapter summaries the main findings of the included studies in this thesis.

5.1.1 Descriptions of the Participants

The mean age of the included 51 dyads was 70.9 (SD=8.5) and 70.7 (SD=9.3) for patients and partners, respectively. The dyads had been living together for an average of 38.4 (SD=14.5) yrs. Other sociodemographic features are presented in table 2.

Table 2 Sociodemographic features		n=51 dyads
	Patient	Partner
Female	22(43.1%)	29(56.9)
Retired n(%)	45(88.2)	39(76.5)
Working* n(%)	10(19.6)	16(31.4)
Level of education n(%)		
Elementary	8(15.7)	6(11.8)
Secondary	11(21.6)	16(31.4)
University	32(62.7)	29(56.9)
Level of income**n(%)		
<199 000	13(25.5)	13(25.5)
200 000-450 000	27(52.9)	30(58.8)
>450 000	11(21.6)	8(15.7)

Values are expressed in total number(n) and percentages (%)

* =Some of the study subjects were still working.

**=Swedish kronor

All PD patients were treated with at least one antiparkinsonian medication and experiences of complications were common: Out of 48 patients 29(57%) experienced motor fluctuations and 33 (65%) experienced dyskinesia. Other clinical characteristics are presented in table 3. In study 1, the sociodemographic and clinical features were slightly different because there were only 50 dyads included in the analyses.

Table 3 Clinical features		n=51dyads	
		Patient	Partner
Total scores MS	m(SD)	3.2(.65)	2.9(.77)
Dimensions of MS			
Love and affection	md(IQR)	3.6(0.67)	3.6(1.0)
Shared pleasurable activities	md(IQR)	3.2(1.25)	3.0(1.25)
Shared values	md(IQR)	3.0(1.0)	3.0(1.5)
Reciprocity	md(IQR)	3.3(1.0)	2.8(1.67)
Mutuality score across H/Y stages (study 1, n=49)			
Stage 1	m(SD)	3.7(0.3)	3.6(0.4)
Stage 2	m(SD)	3.3(0.4)	3.1(0.6)
Stage 3	m(SD)	3.0(0.4)	3.1(0.5)
Stage 4	m(SD)	3.1(0.4)	2.5(0.5)
Stage 5*	m(SD)	2.7	2.2
CBS	m(SD)		42.5(15.8)
PD-duration	m(SD)	8.4(6.4)	
UPDRS III	m(SD)	18.1(5.8)	
NMSQuest	m(SD)	12.1(4.6)	
IQCODE	m(SD)	3.2(.53)	
PDQ8	m(SD)	27.4(14.6)	
Patients self-rating of motor signs			
Tremor	n(%)	28(54.9)	
Bradykinesia	n(%)	43(84.3)	
Rigidity	n(%)	38(74.5)	
Gait	n(%)	35(68.6)	
Dependency in ADL n=35			
Shopping	n(%)	32(91.4)	
Cooking/cleaning	n(%)	28(80.0)	
Walking/transferring	n(%)	23(65.7)	
Bath/showering	n(%)	13(37.1)	
Grooming/dressing	n(%)	11(31.4)	
Toileting	n(%)	9(25.7)	
Food intake	n(%)	7(20.0)	

Notes: PD: Parkinson's disease, MS: mutuality scale, PDQ8: The Parkinson's Disease Questionnaire Summary Index, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, NMSQuest: Non-motor Symptoms Questionnaire, UPDRS III: The Unified Parkinson's Disease Rating Scale-Part III. CBS: Caregiver burden scale, ADL: Activities in daily life, H/Y: Hoehn and Yahr,

* no SD because only one patient was in stage 5. Values are expressed in mean (m) and standard deviation(SD) or median (md) and interquartile range (IQR) or number (n) and percentage (%) as indicated in the table.

Out of 51 patients 35(68.6%) needed supervision or help with ADL and the partner was the main provider of this help (table 4). Even if supervision/help was needed in some activities, the majority 32(63%) was able to be left alone unlimited period of time.

Table 4 Frequency of patients who needs help in different daily activities n=51

	No help		Supervision		Some help		All help	
	n	(%)	n	(%)	n	(%)	n	(%)
Grooming/dressing	40	78.4	6	11.8	4	7.8	1	2.0
Bath/shower	38	74.5	6	11.8	5	9.8	2	3.9
Food intake	44	86.3	2	3.9	5	9.8	0	
Toileting	42	82.4	3	5.9	5	9.8	1	2.0
Walking/transferring	28	54.9	6	11.8	15	29.4	2	3.9
Cooking/cleaning	23	45.1	2	3.9	16	31.4	10	19.6
Shopping	19	37.3	1	2.0	21	41.2	10	19.6

Values are expressed in total number(n) and percentages (%)

According to the result of the NMSQest the most frequently reported symptom was nocturia (78.4%) and delusion (11.8%) was the least frequently reported symptom (table 5)

Table 5 patients self-rated frequency of non-motor symptoms

	n=51
	Yes n(%)
Nocturia	40(78.4)
Urgency	38(74.5)
Dizzy	33(64.7)
Concentrating	28(54.9)
Taste/smelling	28(54.9)
Insomnia	28(54.9)
Restless legs	27(52.9)
Sex difficulty	27(52.9)
Bowel emptying incomplete	26(51.0)
Falling	25(49.0)
Remembering	25(49.0)
Constipation	25(49.0)
Sad, blues	24(47.1)
Dribbling	22(43.1)
Anxiety	20(39.2)
Diplopia	20(39.2)
Swallowing	19(37.3)
Acting out during dreams	18(35.3)
Pains	17(33.3)
Intense vivid dreams	16(31.4)
Sex drive	16(31.4)
Hallucinations	15(29.4)
Sweating	14(27.5)
Loss of interest	12(23.5)
Weight	12(23.5)
Swelling	12(23.5)
Day time sleepiness	11(21.6)
Bowel incontinence	8(15.7)
Vomiting	7(13.7)
Delusions	6(11.8)

Values are expressed in number(n) and percentages (%)

5.1.2 Study 1, Validation of the Swedish Mutuality scale

The scale was independently translated forward and back by two bilingual persons. Minor adjustment according the response format was made to match the Swedish language. In general, translators, the panel of experts, two lay persons and the 50 dyads with one having PD found the translated scale items clear and easy to understand.

Neither floor nor ceiling affect was detected for the highest and lowest item scores in any of the groups.

Psychometric properties were assessed by PCA for the scale answered by the patients and the scale answered by the partners. Initially, the principal extraction indicated a three-component solution in both groups. However, in both groups an inspection of the pattern matrix revealed several complex variables with cross-loading on two components. An inspection of the Catell's scree plots indicated that a two-component solution would be more appropriate (fig 1).

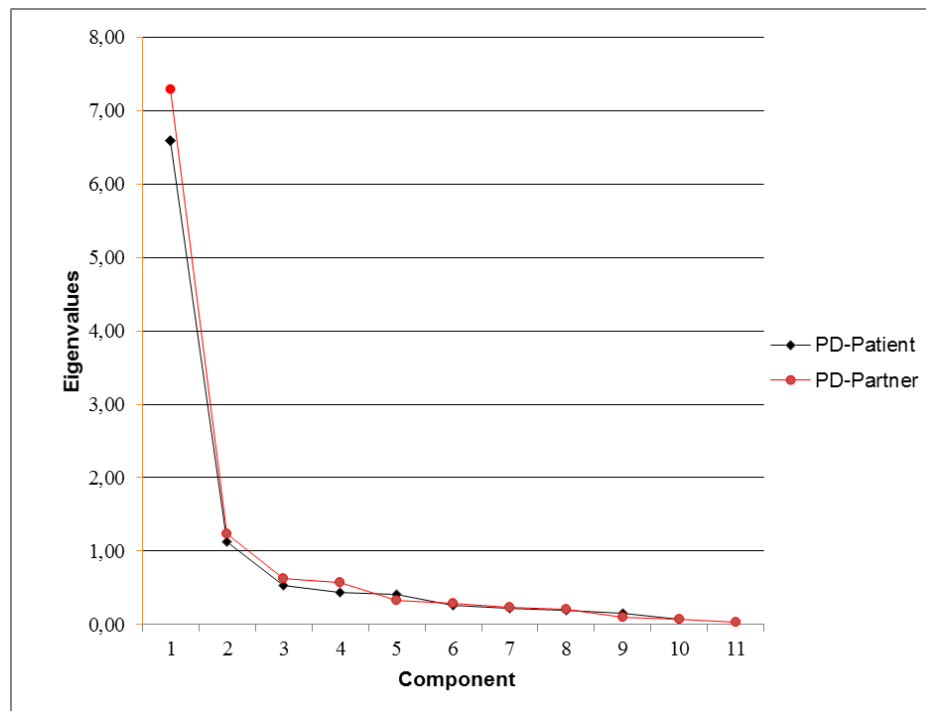


Fig. 1 Patients' and partners' scree plots of eigenvalues and number of components resulted from the principal component analysis

After repeated PCA, 3 items were discarded in the scale answered by partners due to cross-loading items. Comparison of the final two component solutions (patients' and partners' MS scale) revealed that different items loaded on different components meaning that potential "subscales" contained different items in the two groups.

Internal consistency was evaluated by calculating the Cronbach's alpha coefficients for the 15 items MS scores in both groups.

For the 15 items MS scale answered by partners Cronbach's alpha was calculated as 0.933 (95% CI: 0.902-0.958). Cronbach's alpha would not further improve by deletion of any items. Mean inter-item correlation was 0.493.

For the 15 items MS scale answered by patients Cronbach's alpha was 0.936 (95% CI: 0.907-0.960). For the scale answered by patients' deletion of item 6 and 9 would have improved

Cronbach's alpha with 0.940 and 0.939, respectively. For the 15 items scale mean inter-item correlation was calculated as 0.503.

In prior PD studies, inverse correlation between mutuality and caregiver strain have been used as evidence of construct validity (44). Furthermore, a decrease was noted in MS scores across the H/Y stages (51). In the present study, evidence of criterion validity was demonstrated by the findings of a decrease in MS scores across the H/Y stages in both groups (table 3).

5.1.3 Study 2, Determinants of dyadic relationship and its psychosocial impact in patients with Parkinson's disease and their spouses

There were no significant differences between patients' and partners' MS total scores expect for the dimension of reciprocity (table 3). Of the scales' four dimensions, the dimension related to reciprocity was rated higher by patients (median=3.3 vs median=2.8, $p=0.014$).

Bivariate correlations

Spearman rho correlation coefficient was calculated to identify strength and direction of the relationship between potential predictors of patients' and partners' mutuality, patients' HRQoL, and caregiver burden (table 6). Potential predictors with correlation coefficients >0.1 were entered into the regression models. Predictors with suspect multicollinearity problems were discarded one by one and the predictor with highest tolerance and adjusted R^2 value remained.

Table 6 Spearman rank correlation coefficients between independent variables and dependent variables
n=51 dyads

	PD Patient MS		PDQ8		PD Partner MS		CBS	
	Rho	p-value	Rho	p-value	Rho	p-value	Rho	p-value
PD-Patient MS	1.00							
PDQ8SI	-.516	<.001	1.00					
PD-Partner MS	.524	<.001	-.409	.003	1.00			
CBS	-.262	.063	.292	.038	-.631	<.001	1.00	
UPDRS III	-.311	.026	.322	.021	-.255	.071	.286	.042
H/Y	-.290	.039	.413	.003	-.309	.027	.336	.016
NMSQuest	-.178	.212	.631	<.001	-.252	.074	.258	.067
IQCODE	-.229	.107	.285	.042	-.529	<.001	.618	<.001
Cohabitation	.056	.695	-.013	.925	.072	.614	-.296	.035
PD-duration	-.199	.171	.085	.563	-.100	.495	.053	.715

Notes: PD=Parkinson's disease, PDQ8=The Parkinson's disease Questionnaire, MS=Mutuality scale, CBS=Caregiver burden scale, NMSQuest= The Non-motor Symptom questionnaire, UPDRS III= The Unified Parkinson's Disease Rating scale-Part III, H/Y=Hohen & Yahr, IQCODE= Informant Questionnaire on Cognitive Decline in the Elderly

Multivariate regression analyses

Four multivariate linear regression analyses were applied to explore potential predictors of patients' mutuality, partners' mutuality, patients' HRQoL, and caregiver burden.

In the final model with patients' MS as the dependent variable of the included variables explained 31.6% of the variance. Of the included variables, partners' MS score ($\beta=.419$, $p=.002$) and gender ($\beta=.332$, $p=.017$) were the variables that explained most of the variance. In other words, patients' MS scores were higher in those with a male partner and partners with high perceived mutuality.

Using patients' HRQoL as the dependent variable, the included predictors explained 49.7% of the variance. In this model, patients' MS score ($\beta = -.433$, $p=.001$) and NMSQuest ($\beta = .498$, $p<.001$) explained most of the variability. This means that patients with higher perceived mutuality had better HRQoL while increasing frequency of NMS decreased HRQoL.

In the final model with partners' mutuality as the dependent variable, the included predictors explained 28.9% of the variance in partners' MS scores. Patients' MS scores ($\beta = .461$, $p=.002$) and IQCODE scores ($\beta = -.314$, $p=.016$) contributed to most of the explained variance of partners' mutuality. In other words, partners' mutuality was higher in those patients with higher level of mutuality. Furthermore, a decline in cognitive function decreases partners' mutuality.

When caregiver burden was entered as the dependent variable, the explained variance of the included predictors was calculated as 52.7%. An increase on partners' MS scores ($\beta = -.559$, $p= <.001$) decreases caregiver burden. This means that higher level of partners' mutuality may protect and lower the perceived burden. There was a trend towards a negative association between patients' cognitive function and caregiver burden ($\beta = .219$, $p=.050$).

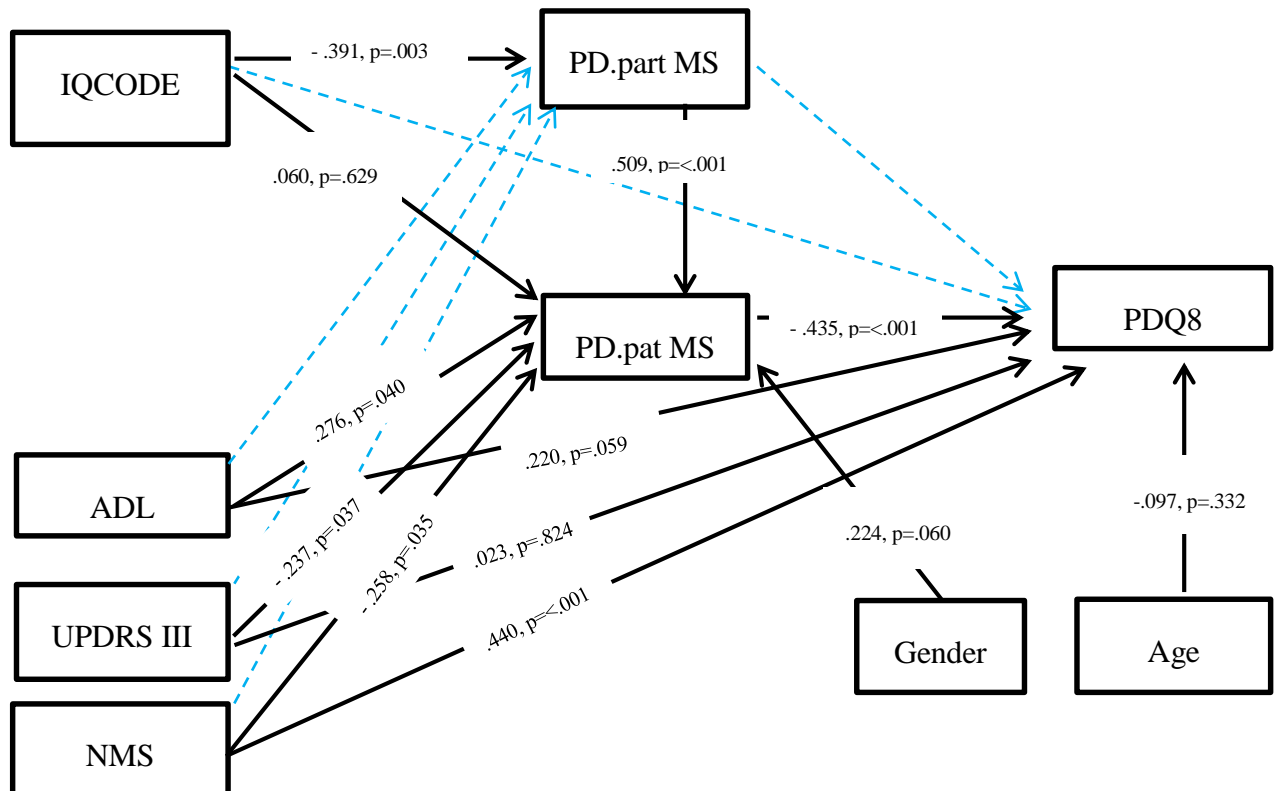
In brief, our findings suggest that PD dyads tend to rate their mutuality high and there was no significant difference between the groups except for the dimension of reciprocity which was rated higher by patients. Furthermore, patients' mutuality and frequency of NMS were associated with HRQoL and partners' mutuality with caregiver burden. Also, perceived mutuality by one member of the dyad seems to be an important predictor of the other members' perceived mutuality.

Altogether the results from the correlation and the regression analyses in study 2 indicated that mutuality might act as mediator on patients HRQoL and caregiver burden. To explore these two mediation hypotheses from the patients' and the partners' perspectives, a decision was made to construct two models using SEM with manifest variables exploring if patients' and/or partners' mutuality mediates the effect of motor, NMS and dependency in ADL on patients' HRQoL (study 3) or caregiver burden (study 4).

5.1.4 Study 3, Mediating effect of mutuality on health-related quality of life in patients' with Parkinson's disease

In this study we hypothesized that motor symptoms, NMS, impaired cognition and dependency in ADL act as primary stressors with direct or indirect effects (mediated) through patients' and partners' mutuality on patients' HRQoL.

The path model with direct effects presented as standardized path coefficients is illustrated in figure 2



Notes: PD: Parkinson's disease, Pat.MS: PD patients' mutuality scale, Part.MS: PD partners' mutuality scale, PDQ8: The Parkinson's Disease Questionnaire, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, NMS: Non-motor Symptoms Questionnaire, UPDRS III: The Unified Parkinson's Disease Rating Scale-Part III, ADL: Activities in daily life (0=independent, 1=dependent), Gender: 0=female, 1=male, Age: PD partners' age.

Figure 2 Direct effects reported as standardized path coefficients for the final model with HRQoL (PDQ8) as the outcome variable. Dashed lines are non-significant direct paths which were removed from in the final model. The best fit of the final path model was achieved with $\chi^2 = 7.980, df=9, CMIN/DF=.887, p=.536, GFI=.968, NFI=.939, CFI=1.0, TLI=1.0$ and $RMSEA=.00$ (95%CI=.00-.146). $n= 51$ dyads

In the first model several of the path coefficients were small and non-significant and were discarded one by one (figure 2). The final model could explain 42.0% of the variance in patients' mutuality, 15.3% in partners' mutuality and 55.8% of HRQoL.

Standardized indirect and total effects are presented in table 7.

Table 7 Indirect and total effect of disease related factors on PD patients' health-related quality of life (Bootstrap sample = 2000).

Effects	Path	Standardized	95% CI		p-value
		path coefficient	Bias-corrected		
Indirect effect with one mediator	ADL→Pat.MS→PDQ8	-.120	-.300	-.014	.079
	UPDRS III→Pat.MS→PDQ8	.103	.010	.239	.026
	NMS→Pat.MS→PDQ8	.112	.006	.263	.043
	IQCODE→Part.MS→Pat.MS	-.199	-.339	-.057	.011
Total effect	ADL→PDQ8	.100	-.115	.351	.335
	UPDRS III→PDQ8	.126	-.116	.334	.372
	NMS→PDQ8	.552	.344	.735	.001
	IQCODE→PD-pat.MS	-.139	-.343	.157	.295

Notes: PD: Parkinson's disease, ADL: Dependency in activities in daily life (0=independent, 1=dependent), Pat.MS: PD patient's mutuality scale, PDQ8: The Parkinson's Disease Questionnaire, Summery Index, UPDRS III: The Unified Parkinson's Disease Rating Scale-Part III, NMS: Non-motor Symptoms Questionnaire, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, Part.MS: PD-partner's mutuality scale.

The mediating test of indirect effects revealed that the effect of NMS (beta=.112, p=.043) and UPDRS III (beta=.103, p=.026) on HRQoL was mediated by patients' mutuality. In other words, increasing frequency of motor and NMS decreases patients' mutuality, in turn leading to worse HRQoL (increasing PDQ8 scores). According to the typology and interpretation suggested by Zhao et al. the significant direct effect of NMS (beta=.440, p=.001) on HRQoL indicates a complementary mediation and point to the possibility of omitted mediators in the model (73). The non-significant direct effect of UPDRS III (beta=.023, p=.883) on HRQoL indicates an indirect-only mediation and implies that the effect of motor symptoms on HRQoL is fully explained by patients' mutuality.

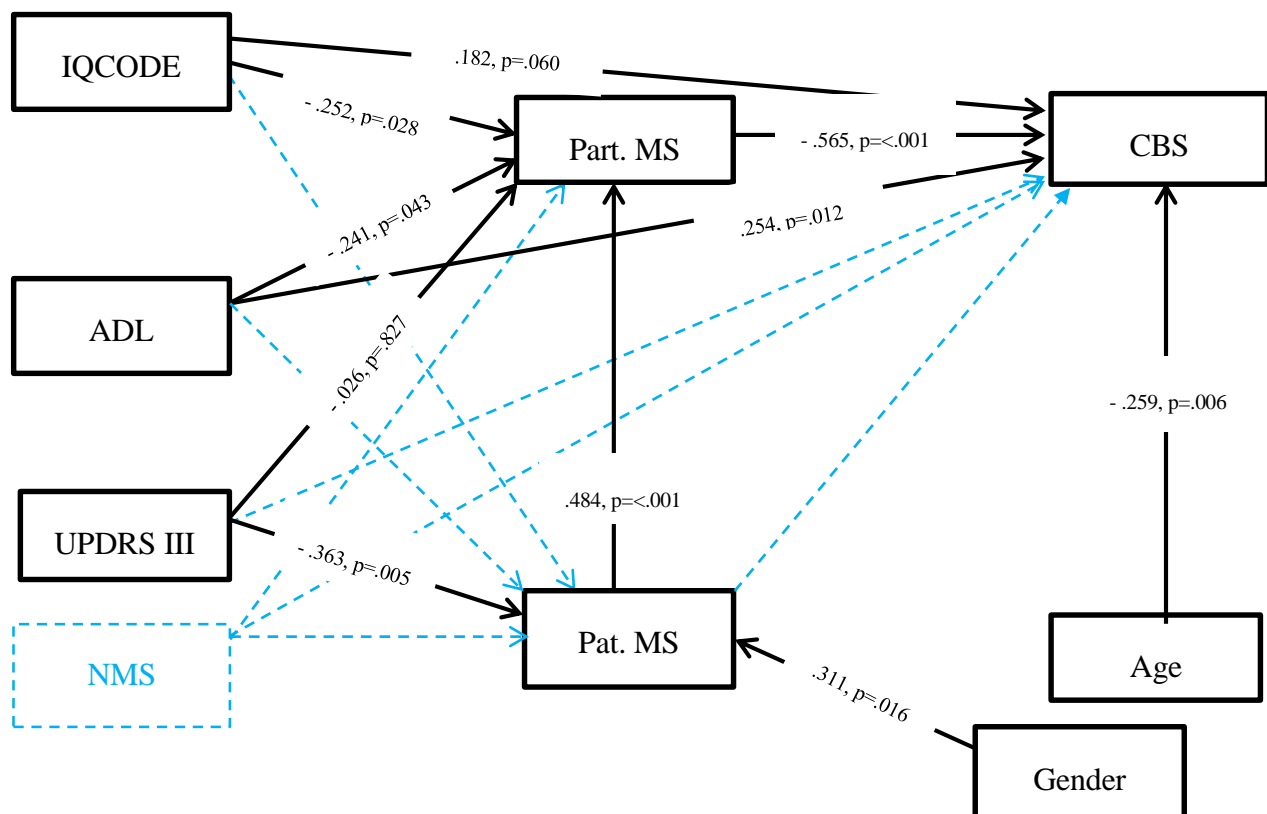
Impaired cognition (IQCODE) was only mediated by partners' mutuality (beta=.199, p=.011). Suggesting that a decline in cognitive functions in patients decreases partners' mutuality in return leading to a decrease in patients' mutuality. The direct effect of impaired cognition on patients' mutuality was not statistically significant (beta=.060, p=.629) pointing towards an indirect-only mediation.

The main findings suggest that increasing severity of motor and NMS decreases patients' mutuality, in turn leading to worse HRQoL. Impaired cognitive function was not mediated by patients' mutuality, instead the effect of impaired cognition decreases partners' mutuality in turn leading to lower patients' mutuality.

5.1.5 Study 4, Mediating effect of mutuality on caregiver burden in Parkinson's disease partners

In this study we hypothesized that motor symptoms, NMS, cognitive impairment and dependency in ADL act as primary stressors with direct or indirect effects (mediated) through patients' and partners' mutuality on caregiver burden.

After excluding several unrequired and non-significant path coefficients one by one the model was better fit (see figure 3).



Abbreviation: PD=Parkinson's disease, Pat.MS= PD patient mutuality scale, Part. MS= PD-partner mutuality scale, CBS: Caregiver burden scale, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, NMS: Non-motor Symptoms Questionnaire, UPDRS III: the Unified Parkinson's Disease Rating Scale-Part III, ADL: Activities in daily life (0=independent, 1=dependent), Gender: 0=female, 1=male, Age=PD partners age.

Fig 3 Direct effects reported as standardized path coefficients for the final model with caregiver burden as outcome. Dashed lines are non-significant direct paths which were removed in the final analysis. The best fit of the final model was achieved with $\chi^2=7.658$, $df=8$, $CMIN/DF=.957$, $p=.468$, $GFI=.965$, $NFI=.938$, $CFI=1.0$, $TLI=1.0$ and $RMSEA=.00$ (95%CI=.000-.161).

Standardized indirect and total effects presented in table 8.

Table 8 Indirect and total effect of disease related factors on caregiver burden.

Effects	Path	Standardized path coefficient	Bootstrap sample = 2000		
			95% CI		p-value
Indirect effect with one mediator	ADL→Part.MS→CBS	.136	.002	- .289	.048
	IQCODE→Part.MS→CBS	.142	.028	- .288	.014
	UPDRS III→ Pat.MS→Part.MS	-.176	-	- -	.006
Total effect			.345	.052	
	ADL→CBS	.391	.165	- .593	.002
	IQCODE→CBS	.324	.071	- .537	.006
	UPDRSIII→Part.MS	-.202	-	- .014	.061
			.422		

Abbreviations: PD=Parkinson's disease, ADL= dependency in activities in daily life (0=independent, 1=dependent), Part.MS: PD partner mutuality scale, CBS=caregiver burden scale, IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly, Pat.MS=PD patient mutuality scale, UPDRS III: the Unified Parkinson's Disease Rating Scale-Part III.

The test of indirect effects revealed that partners' mutuality mediated the effect of dependency in ADL (beta=.136, p=.048) on caregiver burden. Consequently, having a partner who is dependent in ADL may lead to a decrease in partners' mutuality, in turn leading to elevated burden. Additionally, the significant direct effect of dependency in ADL on caregiver burden indicates a complementary mediation and points toward omitted mediators in the model.

The effect of increasing IQCODE scores on caregiver burden was also mediated by partners' mutuality (beta=.142, p=.014). Suggesting that a decline in patients' cognitive function decreases partners' mutuality in turn leading to higher perceived burden. The lack of a significant direct effect of impaired cognition (beta=.182, p=.060) on burden indicates an indirect-only mediation.

Increasing severity of motor symptoms (UPDRS III) was not mediated by partners' mutuality (beta= -.026, p=.827). Instead, the effect of increasing motor symptoms decreases patients' mutuality in turn leading to lower level of perceived mutuality by partners (beta= -.176, p=.006).

The main findings were that the effect of impaired cognition and dependency in ADL decreases partners' mutuality and this leads to higher level of burden. Increasing severity of motor symptoms was not mediated by partners' mutuality, instead the effect decreases patients' mutuality in turn leading to lower perceived mutuality by partners.

6 DISCUSSION

6.1 SUMMARY AND DISCUSSION OF MAIN FINDINGS

Growing evidence suggest that mutuality is a protective factor regarding negative caregiving outcomes, yet research involving patients' perspective of mutuality is still scarce. Since it is reasonable to believe that patients' perceived mutuality is equally important in family oriented care planning, thus filling this gap of knowledge is necessary.

6.1.1 Psychometric properties of the Swedish version of MS

To our knowledge, this is the first study that has tested psychometric properties of the MS in a sample consisted of both PD patients and their partners. Our findings indicate that the Swedish version of the MS has acceptable reliability and validity regarding the scales answered by PD patients and partners. There was a high inter-relatedness of the items within the Swedish MS suggesting that the items measure the same concept (68). In line with our results, psychometric testing of the MS in a sample consisted of stroke patients and their caregivers showed similar Cronbach's alpha with ours (75, 76). Furthermore, in a sample including PD caregivers the alpha value was calculated as 0.95 (51). In the present study deletion of items did not decrease the alpha value except for item 6 and 9 in the scale answered by patients, which indicates that some of the items are redundant and can be discarded. However, discarding items from a scale that already has been used in prior research limits the feasibility of comparing the results between prior studies. Thus, this was not done in the subsequent studies. The reported four dimensions (love and affection, shared values, shared pleasurable activities, and reciprocity) of the original English version of MS was developed through content analyses rather than factor analyses (41, 42). Consistent with prior studies our investigation of MS underlying structure revealed several cross-loading items within the scale (77, 78). Our scales had high alpha values and high inter-item correlation suggesting that mutuality is a narrow concept which may explain why the scale has several cross-loading variables, although it seems like different dimensions or subscales exist. Interestingly, two recently published studies used a different statistical approach exploring the underlying structure of the MS in couples, whereof one in the couple suffered from stroke or heart failure (75, 79). Instead of exploratory factorial analyses used in prior studies including our own, the authors conducted a confirmatory factor analysis which supported the original theorized four-factor structure of the MS in both patients and their caregivers. Overall, more research regarding the existence of subscales is warranted and one direction of future research may be to further explore the four dimensions constructing the scale. Validity, which concerns to what extent a scale measures what it intends to measure was also explored for the Swedish MS (68) Evidence of the MS criterion validity has been

demonstrated by a decline of MS scores across PD stages, which is in line of our results (51). Consistent with prior research and further evidence of construct validity, the results of study 2 showed an inverse correlation between partners' mutuality and caregiver burden (44, 80). A study by Ostwald et al. showed that stroke patients' mutuality was a significant predictor of life satisfaction (a global measurement of quality of life) (53). Since it is not unreasonable to believe that it could be an association between PD patients' mutuality and HRQoL, we can use the results from study 2 showing that higher patients' mutuality is associated with higher patients' HRQoL as an argument for criterion validity of patients' MS. Altogether, our results from study 1 and 2 provide preliminary psychometric evidence that the use of the whole scale in PD patients and partners is appropriate. The findings of cross-loading variables and the differences of item loading on the emerged components in the two groups limit the usefulness of using our two component solutions. Instead, in subsequent studies, when needed, the original four dimensions of the MS were used to discuss the results.

6.1.2 Patients' and partners' mutuality

Similar to prior research the dyads rated their mutuality as rather high (52, 75). In contrast to the result of other studies, there was no significant difference in the total scores between patients and partners except for the dimension of reciprocity, which was lower in the group of partners (52, 75). This may be due to different samples in the reviewed studies where Lyons et al. study had older frail dyads and Pucciarelli et al. had stroke patients and their caregivers, who probably were more dependent in ADL compared to our participants (52, 75). Perhaps patients who need more help in ADL also to a greater extent feel more appreciation and gratification towards their caregivers in turn leading to higher perceived mutuality. In contrast, partners who gradually take on more responsibility of previous shared responsibility, which may lead to lower mutuality.

6.1.3 Patients' mutuality, associated factors and influence on patients' HRQoL

In this section the results of study 2 and 3 are summarized and discussed from the patients' perspective. The aim of the discussion is to disentangle the influence patients' or partners' mutuality has on patients' HRQoL. Furthermore, to discuss underlying mechanisms between clinical variables, mutuality and HRQoL.

The patients participating in this study had well established symptoms of PD at mild to moderate levels of severity according to H/Y (md=2, IQR=1). Even though appraisal, severity of symptoms, and complications were not assessed, patients' frequency of self-reported symptoms and complications indicate that daily life can be problematic for most of the patients which can be illustrated by description by a person with PD in a qualitative interview study:

"It takes time to do the buttons . . . It's irritating sometimes. It takes a long time before you have finished dressing. . . ." (81)

Another description by a person with PD in a qualitative study regarding disability and complications:

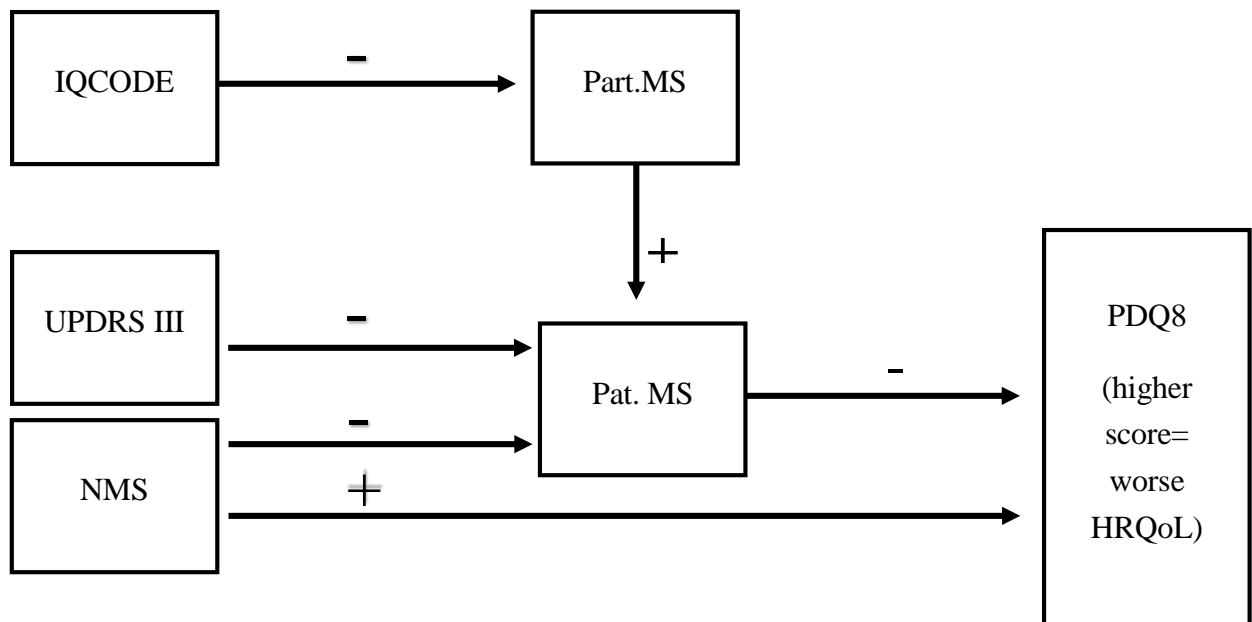
“I couldn’t walk any further than maybe out of the house and into the garden . . . then I found myself in a world that was totally my own . . . I became completely stiff . . . my wife shouted at me that “you have to move”, but I was completely stuck . . .”(81)

Interestingly, even if there was a significant correlation between motor signs and patients’ HRQoL in the subsequent regression analysis, the effect of motor signs on patients’ HRQoL was not proven. Instead, NMS, which often precedes motor symptoms, were shown to negatively affect patients’ HRQoL. Our result are similar to previous research (16, 82-84). In the present study the mean frequency of NMS symptoms was 12 (SD=4.6) and the NMSQuest domains with most frequently reported problems were; urinary (76%), cardiovascular (44%), depression/anxiety (43%), memory (42%) and sexuality (42%), corresponding to previous research (23).

Another interesting finding was that patients’ not partners’ mutuality was the variable with largest influence on HRQoL. This means that patients with higher mutuality are likely to have higher perceived HRQoL compare to those with lower level of mutuality. It implies that supporting PD patients’ to maintain or improve the quality of relationship may help improving patients’ HRQoL. Since growing evidence from caregiver research indicates that caregivers’ mutuality acts as protective factor against different negative caregiving outcomes, our result suggests that patients’ mutuality is equally important to assess (43). Our findings showed that patients’ MS scores were higher in those with a male partner and partners with higher level of mutuality. Overall, research exploring PD patients’ mutuality association with gender and other associated factors is scarce but the result from a previous study can be linked to gender differences in mutuality. In an older study including elderly persons (n=234 dyads), male caregivers were found to have higher level of mutuality compared to female caregivers (85). One suggested explanation to lower level of mutuality in females is that wives take on a more nurturing role in the relationship, spend more time thinking about the relationship and are more concerned around other stressors within the family (86). However, more research is needed regarding gender differences since women’s work role and socio-economic status probably have change for most women during the last decades.

The rationale for testing our mediation hypothesis was based on the results of study 2 and guided by the stress-process models that have been proposed for patients having dementia and caregivers (31, 48, 60). Even though there are differences in the proposed stress-models, a common denominator is that primary stressors (here PD symptoms) may, directly or indirectly, influence an outcome variable (here patients’ HRQoL) through mediators (here patients’ or partners’ mutuality (31, 48, 60). The results indicated that the effects of NMS decrease patients’ mutuality in turn leading to worse HRQoL.

In addition to the indirect effect, a significant direct effect of NMS on patients' HRQoL was found, which suggests a complementary mediation in turn implying that there are omitted variables in the model (figure 4).



Abbreviation: PD=Parkinson's disease, Pat.MS= PD patients' mutuality scale, Part.MS= PD partners' mutuality scale, PDQ8: Parkinson disease questionnaire, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, UPDRS III: The Unified Parkinson's Disease Rating Scale-Part III.

Fig 4 Direction of the included variable and the role of PD patients' and partners' mutuality as a mediator between PD symptoms and patients' HRQoL

This is an important result since it can be used to point out future directions in research according to Zhao et al. (73). According to the described stress process models other variables of interest that may influence mutuality are personality, coping mechanism or external support (60). For instance, in caregiving research it has been suggested that being more optimistic are associated with less burden. (45). Perhaps personality, coping mechanisms and use of external support can be linked to patients' mutuality and HRQoL. NMS such as urinary, cardiovascular, depression/anxiety, memory and sexual function were common symptoms experienced by our PD patients. In addition, according to original MS dimensions scores of patients' shared pleasurable activities and shared values were the domains with lowest scores (table 3). In an attempt to illustrate how our results of the indirect effect can be understood, patients' urinary problems will be used to exemplify this. Urine urgency, which was the most frequently described NMS in our sample, if severe enough, may

result in worries because of uncertainty if and when urgency arises. Fear of leakage, smell or not being able to find a toilet quickly enough when needed, may preoccupy patients' thoughts and impede the possibility of spending time outdoors and engage in joint leisure activities with their partner. Other NMS can in a similar way be expected to negatively influence different dimensions of mutuality.

In contrast to most motor signs several of the NMS are nonvisible and patients' lived experience of them are not always easy to comprehend for others. Even though we have not conducted any qualitative study, one of the participant description of this dilemma was:

"My wife can see and understand the consequences of my PD symptoms. but she can't feel what I feel, because I feel every symptom, every change, every minute, every day, and she doesn't"

Thus, partners may not always be fully aware of how much these problems or issues influence patient's daily life. Lack of awareness or even disagreement how to deal (shared values) with symptoms or consequences of PD symptoms may put a strain on the relationship in turn leading to a decline in HRQoL.

Patients' mutuality was also found to mediate the effect of motor signs on HRQoL. The lack of significant direct effect between UPDRS III scores and HRQoL suggests an indirect-only mediation. In other words, the effect of motor symptoms decreases patients' mutuality in turn leading to a decline of HRQoL. Even though it is impossible to do justice to the reality of how it is to be living with PD. The effect of motor features on the dimension of joint pleasurable leisure activities within MS can be exemplified by a woman with PD in a qualitative study:

"We love to go to car shows. We can't anymore. I can't walk that much. Where they have car shows—I've got a wheelchair, but you can't take it a lot of places." (59)

In contrast to previous research impaired cognition did neither directly affect patients' mutuality nor patients' HRQoL(16, 17, 87, 88). Instead, the test of indirect effects revealed that the effects of impaired cognition decreased partners' mutuality and the combined effect decreased patients' mutuality. It is possible that the decline in cognitive function was not severe enough to influence patients' HRQoL which relates to the result of Lawson et al., showing a corresponding decline in HRQoL with the level of cognitive function in early PD patients (21). Another explanation is that that cognitive function and its consequences were assessed by partners' and not by the patients' themselves. It could mean that partners' may take over chores and responsibility as they gradually suspect a decline in cognitive function and sometimes the decline only requires reminders or supervision from the partners. Thus, the decline may not be obvious or visible and perhaps most of the patients' still feel involved in day to day decisions and not being excluded from the partnership.

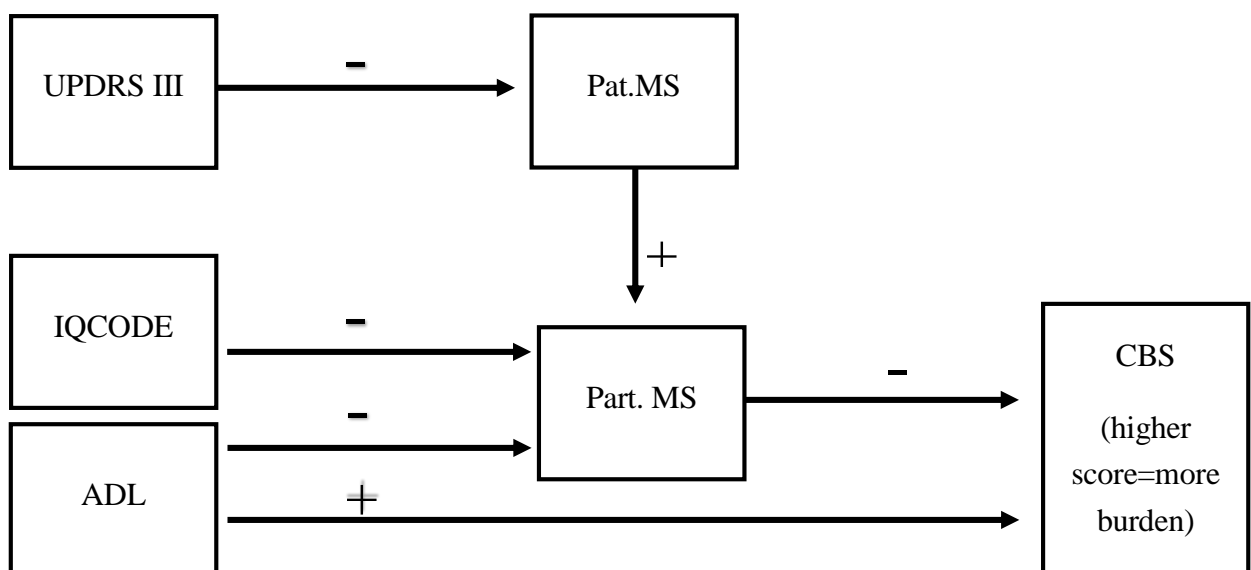
6.1.4 Partners' mutuality, associated factors, and influence on caregiver burden

In contrast to the previous section the result will now be discussed from the perspective of being a partner. In this section by reviewing the results of study 2 and 4, the aim of the discussion is to disentangle the influence partners' and patients' mutuality has on caregiver burden and associated factors. Another aim is to discuss underlying mechanism between the included clinical variables, mutuality, and caregiver burden.

We found that higher level of partners' mutuality was associated with less caregiver burden which is in line with prior studies (44, 48, 51). The protective effect of partners' mutuality on caregiver burden implies that supporting PD partners to maintain high mutuality or improve mutuality may mitigate their experience of burden.

According to prior studies impaired cognition is associated with elevated burden (11, 89, 90). However, in our study the effect of cognitive decline had a larger influence on partners' mutuality than on caregiver burden. Furthermore, patients' mutuality contributed significantly to the variance in partners' mutuality.

Our results indicated that partners' or patients' mutuality may explain (mediate) some of the clinical variables' effect on caregiver burden which are presented in figure 5.



Abbreviation: PD=Parkinson's disease, Pat.MS= PD patients' mutuality scale, Part.MS= PD partners' mutuality scale, CBS: Caregiver burden scale, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly, UPDRS III: The Unified Parkinson's Disease Rating Scale-Part III, ADL: activities of daily life 0= independent, 1=dependent.

Fig 5 Direction of the included variable and the role of PD partners' and patients' mutuality as a mediator between the included variables and caregiver burden

The test of indirect effects revealed that being dependent in ADL (patient variable) decreases partners' mutuality in turn leading to elevated caregiver burden. The existence significant direct effect of ADL on caregiver burden suggested a complementary mediation, implying that there are omitted variables in the model which also contribute to the explanation of the underlying mechanism. Partners' perceived health, personality, coping mechanism, perceived external support may be other variable influencing partners' mutuality. In caregiving research being more optimistic has been linked to less strain (45). Coping mechanism is another variable that have linked to caregiver burden (11). Perhaps more optimistic partners uses more effective coping strategies which improves perceived mutuality in turn leading to less perceived burden.

To illustrate the effect of dependency in ADL may have on the dimension of shared values, a quote from a caregiver of a PD patient in a qualitative interview study will be used as an illustration:

“He doesn...t want to let anybody really help and so we get into sort of a big to-do about that..so I am very tearful today and it...s just, it...s just not good. I mean, you get to the point that you feel like you just want to give up and just say, okay, you think you can handle it all on your own, you just go ahead and do it...I'm getting to that point....”(58)

Furthermore, the effect of decline in cognitive function decreased partners' mutuality and the combined effect increases perceived burden. This type of indirect effect implies an indirect-only mediation. The experience of impaired cognition and the influence it has on the dimension of reciprocity and possibly shared values within the MS can be illustrated by the quote of a caregiver having a husband with PD dementia. Even though the patients in our sample were not diagnosed with dementia and most of the partners did not regard them self as caregivers, this illustration resembles some of the stories told by the participants in the present project:

“It's that change from that dual partnership of having that rock beside you to being the carer really and it changes the balance obviously in the relationship which you will know from everybody else, that's hard actually to deal with and try, not to mask it but to try, you use up a lot of energy trying to make things better, to try and regain that balance, you know, and sort of refocus it, to try and help self-esteem and keep trying to keep, almost maintain the status quo, but it's not.”(91)

Mutuality as a mediator has been explored by other researchers (48, 92, 93). For instance, in samples of frail elderly the effect of behavioural problems related to impaired cognition increased the perceived overload because relationship quality suffers (92). Similar results

were found in a sample included PD caregivers (48). This relates to our results that decline in cognitive function can put a strain on the relationship.

Neither motor nor frequency of NMS influenced partners' mutuality. Instead motor symptoms decreased patients' mutuality in turn leading to lower level of partners' mutuality.

One explanation might be that motor and NMS do not per se influence partners' mutuality. Instead, when motor and NMS impinge on partners' life-space, they are more likely to influence partners' mutuality. However, when motor symptoms negatively influence patients' mutuality it decreases partners' mutuality.

6.1.5 Summary of models

The results from both models suggest that partners' and patients' mutuality mediates some of the included variables in the hypothetical models. Interestingly, the results suggest that motor and frequency of NMS seem to be an important contributor to the decline in patients' mutuality while decline in cognitive function and dependency in ADL contributes to a decrease of partners' mutuality. The results may reflect the visibility and non-visibility of PD symptoms and implies that it is important to investigate how both members of the dyad experience PD symptoms and consequences of living with PD. For instance, PD symptoms such as intermittent tremor, slowness, dizziness, urgency, dribbling, constipation, blurred vision, if not severe enough, are probably not always visible for the partners as they are for the patients. Depending on the situation, they can be both inconvenient and demanding. Likewise, PD symptoms that lead to dependency are probably visible. Even if early cognitive decline may not always lead to dependency it can lead to a need of reminders and controlling which may influence partners' mutuality. Setting regular family meetings with both patients and partners and discuss how PD symptoms affect both members of the dyad may be helpful to detect dyads with low mutuality and personalize interventions. It could enhance both members understanding how PD affects the other member of the dyad and how they cope, maybe strengthen the relationship (59, 94)

6.2 METHODOLOGICAL CONSIDERATIONS

We do acknowledge that there are several limitations of this project. One major obstacle is the cross-sectional design meaning that assumptions regarding causality cannot be made. Thus, our results are mostly concluded on correlations and associations. However, statistical mediation analyses are conceptually based on theory of causality, but rather than testing causality the result suggests that the independent variable affects the mediator which in turn affects the outcome variable (95). Therefore, the proposed stress-process models were used to determine which variable was the most probable and useful way of conceptualising the relationship between independent variables, mediators and outcome variables. Even though mutuality has been proposed as a mediator in several stress-process models, longitudinal studies are needed to increase understanding regarding changes of mutuality in PD dyads (31, 48, 93). This might help proving causal relationship regarding partners' and patients' mutuality i.e. when, by whom, and why do mutuality decrease.

Another limitation is the relatively small sample size for statistical methods such as PCA since a small sample may induce less reliable correlation coefficients. In PCA, a smaller sample size can be adequate when there is strong correlations, high communalities and fewer components which correspond to our analyses (67, 96). Using SEM in mediation analyses in small samples increases the likelihood to identify more indirect-only mediation than complementary mediation (97). A moderate sample size can, however, be adequate if the main objective is to just identify an indirect effect without focusing on type of mediation(97). Focusing only on type of mediation, especially a desire of reporting indirect-only mediation can constrain further theory development. The arguments of Rucker's et al. are in line with our results meaning that it is difficult to claim that there cannot be other variables which influence mediators and outcome variables (97). This leads us to another limitation namely that we have only used disease related variables in our models reflecting the relatively low explained variance, the results of our mediation analyses indicating that there are omitted variables in our models. However, one advantage of using SEM is that direct and indirect effects can be tested simultaneously within the model instead of using several regression analyses and stepwise test direct and indirect effects (98). Future research would benefit from including caregiver variables such as perceived health, perceived support or type of personality. Another approach which explores dyadic coping and interaction could also add new knowledge regarding predictors and underlying mechanisms.

Another limitation is that no test-retest was conducted of the Swedish version of MS to determine the scale's internal consistency over time which could have improved the reliability of the scale. Thus, we cannot be certain that the Swedish MS provides consistent scores over time. On the other hand, this has been provided in several prior studies in different contexts (75, 77, 78).

Also, the included dyads had a predominance of elderly PD patients with mild to moderate PD. Thus, our results cannot be generalized to other groups' e.g. younger dyads or adult children who are informal caregivers. On the other side, including younger dyads or adult children may result in a sample that is too heterogeneous and it can be difficult to compare such results with previous research and between groups. Nonetheless, future research would benefit from a larger sample size including patients in different stages of PD and exploring mutuality in different samples.

Most of the questionnaires in this thesis are widely used in PD research. However, PDQ8 claims to be measurement of PD specific HRQoL but it has been criticized for not measuring sexuality or sleep quality (18, 99). However, it is widely used, and the advantage is that it enables us to compare our results with previous research. The NMSQuest measures frequency of NMS but not severity, which is an important factor since severity may have a larger influence on HRQoL than frequency.

7 CLINICAL IMPLICATIONS

The results may add useful knowledge to person centred care regarding PD dyads. The Swedish MS may be a useful tool that can be used in research and in clinical setting to evaluate perceived mutuality. The original proposed dimension within the MS could be used as a starting point for discussion how PD symptom influence joint activities or shared values. However, having love and affection as a starting point may upset dyads since most dyads love each other in one way or another and this was also the dimension with highest scores in our samples. Our results suggest that clinicians should have both an individual and dyadic perspective in this issues since motor and frequency of NMS seem to contribute most to reduced HRQoL. This being due to that patients' mutuality suffers while dependency in ADL and decline in cognitive function contributed most to elevated burden because partners' mutuality suffers. However, clinicians should also be aware of the notion that, if one member of the dyads seems to have low mutuality, it is likely that it will influence the other members' mutuality.

8 FUTURE RESEARCH

Based on our findings, more research is needed to get a deeper understanding regarding the significance of mutuality when one in the dyad has PD.

1. More research regarding the Swedish MS reliability over time (test-retest), performance in different settings, and existence of subscales are recommended.
2. Using a larger sample size, including both patients' and partners' variables such as severity of motor and NMS, perceived health, perceived external support, coping skills or benefits of living with PD such as personal growth are recommended. Exploring the association between mutuality and other outcome variables could improve the possibility to detect risk dyads.
3. Longitudinal studies aiming to explore if, how, and by whom changes of mutuality take place. Furthermore, to explore if changes are associated with different predictors and the chosen outcome variable. The results could improve the possibility to detect risk dyads and personalize interventions.
4. Future intervention studies designed to maintain or improve mutuality by improving coping skills or perceived benefits/personal growth are another direction of future research that may improve adjustment and wellbeing of dyads.

9 CONCLUSION

The result of this project extended previous research and provided a novel insight on the association between mutuality and clinical variables, patients' HRQoL, and caregiver burden. Another important result from our findings is that new research questions also arose which could be a base for future research.

Summary of the major findings:

- The Swedish version of MS is a user friendly measurement with acceptable psychometric properties, even though more research is needed regarding the existence of subscales and reliability over time.
- Partners with high level of mutuality are likely to experience less burden compared to those with lower mutuality
- Patients with high level of mutuality are likely to have better HRQoL compared to those with lower mutuality
- The level of mutuality perceived by one member of the dyad seems to be a dominant contributor to perceived mutuality by the other member of the dyad.
- When dependency in ADL or decline in cognitive function is present in everyday situations/care situations, caregiver burden increases because partners' mutuality suffers.
- When motor signs and NMS influence everyday situations/care situations, patients' HRQoL deteriorates because patients' mutuality suffers.

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